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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,872	10/22/2003	Jane Hirsh	73690.000120	6830

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,872	HIRSH ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-12,14,16,17,19-21 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6-12, 14, 16, 17, 19-21 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 5/13/2009, in reply to the Office Action mailed 11/13/2008, is acknowledged and has been entered. Claims 1 and 3 have been amended. Claims 29 and 30 are newly added. Claims 1,3, 6-12, 14, 16, 17, 19-21 and 28-30 are pending and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but they are not persuasive, for reasons set forth hereinbelow.

Declaration under 37 CFR 1.132

The declaration under 37 CFR 1.132 filed 5/13/2009 is insufficient to overcome the rejection of claims the pending claims based upon the Midha and Ansseau references as set forth in the last Office action because: It refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 6-10 and 16-17 and 19-21 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137), for reasons set forth in the previous Office Action.

Claims 1, 3, 6-12, 16-17 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137), further in view of Pailard (US 6,699,506), for reasons set forth in the previous Office Action.

Claims 1, 3, 6-12, 14, 16, 17 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137), further in view of Rao (US 2003/0203055), for reasons set forth in the previous Office Action.

Claims 1, 3, 6-10 and 16-17 and 19-21 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476), in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137) and Neliat *et al.* (*Neuropharmacology,*

35, 1996, p. 589-593*)*, further in view of Devane (US 6,228,398), for reasons set forth in the previous Office Action.

Claims 1, 3, 6-10 and 16-17 and 19-21 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476), in view of Ansseau (*Psychopharmacology*, 1994, 114, p. 131-137) and Neliat *et al.* (*Neuropharmacology,* 35, 1996, p. 589-593*)*, further in view of Watanabe (US 7,008,640), for reasons set forth in the previous Office Action.

Response to Arguments

Applicant argues on pages 9-11 of the Response that claim 1 as amended recites two separate releases of milnacipran, the first occurring immediately and a second occurring 3 to 10 hours following oral administration of the formulation, and asserts that this language reflects that although the drug is released substantially immediately upon ingestion, absorption of the drug occurs over a period of time following release. Applicant asserts that although not explicitly recited, there is likewise an absorption timeframe following the second release at 3 to 10 hours, wherein the drug is present in the GI tract and available for absorption which occurs for a period of five or more hours. Applicant asserts that in reciting a 3 to 10 hour release of the second dose, the claim necessarily requires that a significant amount of the milnacipran be absorbed colonically. Applicant refers to the Keller declaration, and argues that the claimed pulsatile formulation delivers milnacipran for the entire period of 3 to 8 or 9

hours following oral administration, and that this time period is encompassed by the claimed period of 3 to 10 hours, and that during that period milnacipran is being absorbed.

This is not found to be persuasive. Given the broadest reasonable interpretation of the instant claims, colonic absorption is not necessarily required by the instant formulation. With regard to the delayed release dosage unit a "second dose of milnacipran that is released 3 to 10 hours following oral administration of the formulation" is required. However, such language can be interpreted such that release may occur at any point in the 3 hour to 10 hour window (e.g. a short burst of release at 3 hours, for example); such language does not necessarily require continuous release over the entire 3 to 10 hour time period, thus colonic abosorption is not a requirement of the instant claims, as alleged by Applicant. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant asserts on pages 11-13 of the Response that it is known that lipophilic drugs would be expected to be absorbed well in the colon, and that lipophobic drugs would not be expected to absorb in the colon, and that Midha teaches pulsatile release of methylphenidate, a lipophilic drug. Applicant refers to the Fleming Declaration, citing that methylphenidate, ketoprofen and ibuprofen are lipophilic drugs; and that milnacipran is a lipophobic drug having a half-life which is over three times longer than methylphenidate. The Declaration also refers to recitation in the claim of release at three to ten hours following administration means that the drug is absorbed during the

period in which it is in the colonic region, and that one would not expect lipophobic milnacipran to absorb in the colon.

While the Declaration has been fully considered, it is not deemed to be persuasive to overcome the rejection. Regarding the half-life of milnacipran, Ansseau teaches the relatively short half-live of milnacipran such that twice-daily administration is required. The Midha reference teaches formulations which are capable of achieving a once-daily administration of drugs which normally require two separate doses, and benefits associated therewith, and methods of preparing such formulations using various delayed release polymers. In response to the argument that one of ordinary skill would not expect to formulate milnacipran to be released in the lower GI tract, Applicant is directed to the Paillard reference. Paillard intends that 70-90% of the milnacipran is released in 8 hours, 80-100% of the drug is released in 12 hours (claim 1). Therefore, it appears that Paillard intended for at least some portion of the drug to be released at later times, which would be consistent with the lower GI tract. Why would Paillard intend to release milnacipran at 8 hours, or 12 hours if it was not expected to absorb? Furthermore, the instant claims do not necessarily require colonic absorption, as set forth above.

With regard to the Paillard reference, Applicant argues on pages 13-14 of the Response that Paillard teaches miltiparticulate extended release milnacipran formulations, and makes no mention of delayed release formulations. Applicant asserts that a close reading of Paillard discourages the skilled artisan from releasing milnacipran slowly from a dosage form. Applicant asserts that Paillard identifies three

formulations which do not release between 10-55% of the dose in 2 hours as "not making it possible to achieve the abovementioned objective in vitro." Applicant asserts that the representative in vitro dissolution profiles encompassed by the instant claims is shown in Figure 1 on page 36 of the Keller declaration, and that none of those formulations release more than 10%, let alone 55% in two hours.

This is not found to be persuasive. Figure 1 of the Keller declaration refers only to part of the dosage encompassed by the instant claims (i.e. delayed release portion), the instant claims also require an immediate release portion which releases from 0.5 to less than approximately 3 hours." With regard to Applicant's assertion that Paillard discourages slow release of milnacipran which is consistent with wisdom at the time the claimed invention was made, such that one would have wanted to release hydrophilic/lipophobic milnacipran relatively quickly (e.g. 10-55% in the first two hours) because they would have known that lipophobic drugs are absorbed best in areas of the higher GI tract. This is not found to be persuasive. Applicant has not taken into consideration the release of the remainder of the drug release after two hours in the Paillard teaching. For example, Paillard intends that 70-90% of the drug is released in 8 hours, 80-100% of the drug is released in 12 hours (claim 1). Therefore, it appears that Paillard intended for at least some portion of the drug to be released at later times, which would be consistent with the lower GI tract. Why would Paillard intend to release milnacipran at 8 hours, or 12 hours if it was not expected to absorb?

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6-12, 14, 16, 17, 19-21 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a milnacipran formulation that provides pulsatile release of milnacipran wherein the formulation comprises a) an immediate release solid dosage unit comprising a first dose of milnacipran that is released substantially immediately following oral administration of the formulation to a patient, resulting in a first plasma level peat at a time between approximately 0.05 hours to less than approximately 3 hours following oral administration. The claims are indefinite, in particular, because the claims recite, “less than approximately 3 hours”. However, “less than” implies a value smaller than a definite value, whereas “approximately” encompasses other values “close to” 3 hours. Therefore, it is unclear what definite value the approximately 3 hours which release is to be less than, and thus the scope of the claims are not clearly defined. The specification does not provide guidance as to what is encompassed by the phrase, as "approximately” is not clearly defined, nor does the phrase “less than approximately” appear to be present in the specification as originally filed.

Claims 29 and 30 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Midha (US 6,340,476) in view of Ansseau (*Psychopharmacology*,

1994, 114, p. 131-137), further in view of Paillard (US 6,699,506), for reasons set forth in the previous Office Action.

With regard to the limitation of claim 30 wherein the delayed release polymer is a methacrylic acid-methyl methacrylate copolymer soluble at pH 6.0 or above, Midha and Paillard both teach acrylic copolymers and methacrylic copolymers as suitable delayed or extended release polymers (see Midha column 5, lines 40+; Paillard column 6, lines 50+).

Double Patenting

Claims 1, 3, 6-12, 14, 16, 17, 19-21 and 28-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 11/192,697, for reasons set forth in the previous Office Action.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS